PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

26 JUL 2004

Applicant's or agent's file reference PCT 1799-019/hj	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/00808	International filing date *(day/month/year)* 27.01.2003	Priority date *(day/month/year)* 29.01.2002
International Patent Classification (IPC) or both national classification and IPC C07C237/42		
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of three sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.08.2003	22.12.2003
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Heibl, C Telephone No. +49 89 2399-8331

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-33
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-33
	No:	Claims	

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/00808

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-14, 16-294	as originally filed
15	received on 03.12.2003 with letter of 03.12.2003

Claims, Numbers

1 (part), 2-15, 16 (part), 17-33	as originally filed
1 (part), 16 (part)	received on 03.12.2003 with letter of 03.12.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

Re Section V----------

(The numbering of the prior art documents (D1,D2..) cited hereinafter corresponds to the order in which they are mentioned in the International Search Report.)

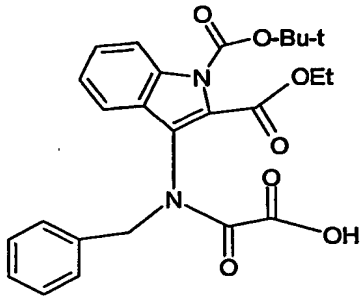
The present invention provides N-disubstituted oxamic acid derivatives as defined in formula (1) which are particularly useful in the treatment of type II diabetes, obesity or the regulation of appetite.

The only pre-published document cited in the search report relating to compounds having the same pharmaceutical use is D2. The present compounds structurally differ from the compounds disclosed in D2 at least by having a $-C(R^{2a})(R^{2b})$ moiety, which is neither taught nor suggested in D2.
Documents D3 to D5 relate to (intermediate) compounds for which no or a different biological activity or medical use is reported. A few compounds concretely disclosed in said documents are excluded from the present claims by way of disclaimer (cf. the *provisos* in claims 1 and 16).

In view of the given pre-published prior art, the subject-matter of present claims 1-33 is considered to meet the requirements of Art. 33(2)-(4) PCT.

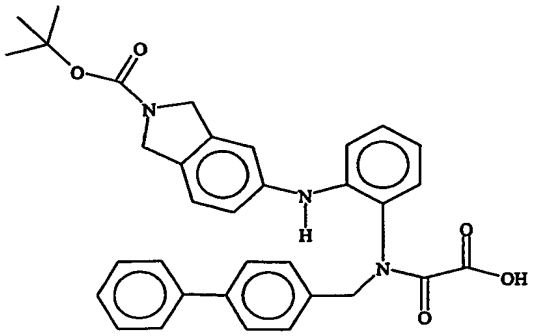
activated blood coagulation factor X and are said to be useful as an antithrombotic agent.

b) A compound of formula (I), wherein Cy is a phenyl group, R^{2a} and R^{2b} are each H, R^1 is an indole moiety substituted in 1-position with an ethyl carboxylate group and in 2-position with a tert.-butyl carboxylate group.



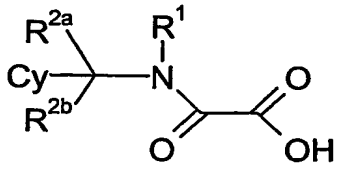
The above single compound is disclosed in EP-483881 (Merrel Dow Pharmaceuticals) and is said to be useful for the treatment of neurodegenerative disease states.

c) A compound of formula (I), wherein Cy is a biphenyl group, R^{2a} and R^{2b} are each H, R^1 is a phenyl group ortho-substituted with a tert-butyl 5-aminoisoindoline-2-carboxylate.



Claims

1. Substituted methylene amide derivative of Formula (I) :



(I)

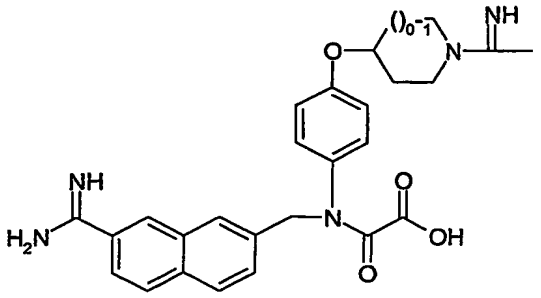
as well as its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts and pharmaceutically active derivatives thereof, wherein

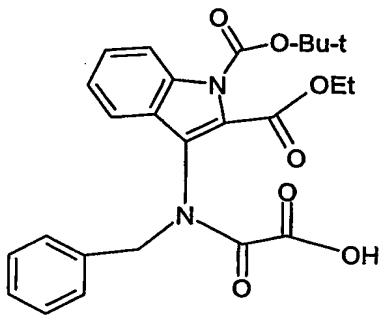
R^1 is selected from the group consisting of (C_1-C_{15})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, aryl, heteroaryl, (3-8-membered)-cycloalkyl or heterocycloalkyl, (C_1-C_{12})alkyl-aryl or (C_1-C_{12})alkyl-heteroaryl, (C_2-C_{12})alkenyl-aryl or -heteroaryl, (C_2-C_{12})alkynyl-aryl or -heteroaryl;

R^{2a} and R^{2b} are each independently from each other selected from the group comprising or consisting of H or (C_1-C_{12})alkyl;

Cy is an aryl, heteroaryl, cycloalkyl or heterocycle group,

with the proviso that the following compounds are excluded :





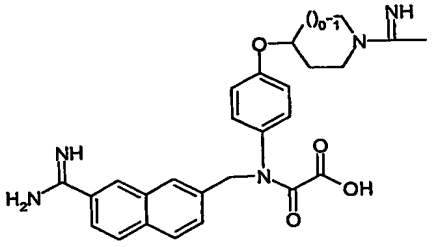
as well as its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts and pharmaceutically active derivatives thereof, wherein

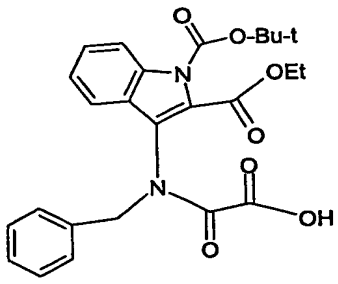
R^1 is selected from the group consisting of $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, aryl, heteroaryl, (3-8-membered)cycloalkyl or heterocycloalkyl, $(C_1\text{-}C_{12})$alkyl-aryl or $(C_1\text{-}C_{12})$alkyl-heteroaryl, $(C_2\text{-}C_{12})$alkenyl-aryl or –heteroaryl, $(C_2\text{-}C_{12})$alkynyl-aryl or –heteroaryl;

R^{2a} and R^{2b} are each independently from each other selected from the group comprising or consisting of H or $(C_1\text{-}C_{12})$alkyl;

Cy is an aryl, heteroaryl, cycloalkyl or heterocycle, for use as a medicament,

with the proviso that the following compounds are excluded :





17. Substituted methylene amide derivative according to claim 16 wherein

R^{2a} and R^{2b} are each H;

R^1 is–CH_2-A, with A being phenyl or thienyl, optionally substituted by cyano, halogen, methoxy, hydroxy, phenoxy, -NO_2, trifluoromethyl;